CHAPTER-V

This chapter deals with the investigation of anti-inflammatory activities of mixed ligand Fe(II), Co(II), Ni(II) and Cu(II) complexes with PIROXICAM, ISOXICAM, ASPIRIN and DICLOFENAC. The biochemical effects of these complexes were studied on albino rats.
5.1 INTRODUCTION

Biological activity of the drug is not the sum of the activities of groups or atoms present in it but due to molecules as a whole. The idea about structure-activity relationship underwent gradual changes with the advancement in the knowledge of chemical and physical properties of the molecules. It is assumed that the pharmacological activities is a function of the physical properties if it is a "structurally non-specific drug" or chemical properties if is "structurally specific drug". The structure is then modified in the following manner to affect the properties:

(I) Shifts are made in the position of functional groups
(II) Valence bonds are saturated
(III) Acidity or basicity is modified.
(IV) Variations of configuration about asymmetry centers are made.

A correlation between the pharmacological action and the structure in a series of compound is its structure activity relationship (SAR). A slight alternation in this structure might totally change a particular effect observed in the parent molecules. Even the most advanced and carefully considered theories have not revealed regularities in the relation of chemical structure to physiological action which could be used indiscriminately in one series of compounds after proving their value in the other. According to W.A. Sexton, physical and chemical activity of a molecule after a structural variation may cause change in distribution in the cells and tissues and access the active site of enzymes and receptors in reaction rates and in excretion patterns. Thus in evaluating structure
activity relationship, the total picture of steric factor, electron density, localization and resultant chemical and physical activities of a given compound need to be considered.

Chemotherapeutic value of a compound is usually determined in different stages. First the preliminary in-vitro tests are performed and if the compounds are found active in such a test, these are then subjected to in vitro tests to determine their toxicity in order to find their possible practical usefulness. As a drug various physico-chemical parameters influence the biological parameters of a drug and even above that structural variation may increase the therapeutic value of the compound by widening the gap between the therapeutic action and its side effects. In addition, certain structural modification may enhance or uncover many dormant physiological and biological efficiency of the drug.

5.2 ANTI-INFLAMMATORY ACTIVITY: INTRODUCTION

Inflammation is a disease condition in which body tissues are affected by heat, redness, swelling and pain. John Hunter (1728-1793), one of the early English physicians to scientifically study the reaction described inflammation as such. This operation of the body termed inflammation requires our greatest attention, for it is one of the most common and most extensive in its effect of any in the animal body.

Inflammation is a response of the tissue to an infection, irritation of foreign substance. It is a part of the host defense but when the response become too great, it may be for worse than the disease state, which is counteracted, and in extreme case, it may be fatal.
The inflammatory process involves a series of events that can be elicited by numerous stimuli, i.e. antigen-antibody interaction, infection agent and thermal or other physical injury. Each type of stimulus provokes a characteristic pattern of response. The response is usually accompanied by the familiar clinical symptoms of erythema, edema, tenderness and pain. Inflammatory responses occur in three distinct phases, each apparently mediated by different mechanisms.

(i) An acute transient phase characterized by local vasodilatation and increased capillary permeability.

(ii) A delayed sub-acute phase, most prominently characterized by infiltration of leukocytes and phagocytic cells.

(iii) A chronic proliferative phase in which tissue degeneration and fibrosis occur.

An obstacle of the discovery of new drugs to treat chronic conditions such as rheumatic disease is the difficulty in developing animal’s models that resemble the disease sufficiently for pharmacological testing. The most widely used primary test to screen new non-steroidal anti-inflammatory agents measures the ability of a compound to reduce local edema induced in the rat paw by infection of the irritant carrageenan, which is a mucopolysaccharide derived from Irish sea mass, chondrus crispus. Most clinical useful anti-inflammatory agents suppress this type of edema. The anti-inflammatory properties of indomethacin, a widely used non-steroidal anti-inflammatory agent, initially detected by a carrageenan assay. Indomethacin is highly potent anti-inflammatory drug but exhibited high degree of gastric toxicity.
advent of propionic acid derivatives in the horizon of anti-inflammatory therapy brought never hopes in the minds of the clinicians starting with ibuprofen, fenoprofen, ketoprofen etc., which were found to be safe drug.

Despite extensive research in the field of inflammation search for an ideal anti-inflammatory agent, devoid of undesirable side effects, still continues. The common set hazard of these agents is the occurrence of gastric irritation or ulceration, especially when in chronic use. Although parallelism seems to exist between the anti-inflammatory and ulcerogenic activity of anti-rheumatic drugs; ibuprofen, fenoprofen and others claimed to have less of such toxicity. Diclofenac sodium is well tolerated compared with others NSAIDs and no other agent of this class appears to have a safety profile that is clearly superior to diclofenac sodium. Diclofenac sodium is rarely or never associated with some other serious side effect caused by other NSAIDs eg. pancreatitis, aseptic meningitis, severe cutaneous or phototoxic reactions. It caused gastrointestinal tract disturbances, peptic ulcer and gastrointestinal tract bleedings. The side effects and edema, skin sashes, dizziness, drowsiness, depression, headache, jaundice and bleeding tendency. The most common side effect of acidic NSAIDs in man, as well as in animals, are gastrointestinal symptoms, i.e. mucosal damage, bleeding and ulceration.

The metal complexes have been reported to play an important part in biological activity of drugs. The participation of the metalloproteins in respiratory, photosynthetic, nitrogen fixation, biosynthetic and metabolic processes is essential to the foundation of life. Several cobalt
complexes are important as model of the metal to oxygen bonding that is involved in biological systems. Cobalt is a constituent of vit.B$_{12}$. Protein containing iron participates in oxygen transport. A number of copper proteins including enzymes have been reported $^{17}$.

A variety of recent observations indicated that copper complexes, when administered in conjugation with anti-inflammatory drugs, exhibit synergistic activity $^{18}$. Copper has been shown to suppress inflammation and to possess anti-ulcer properties $^{(19-20)}$. Fe, Co and Cu chelates of anti-inflammatory agents are known to be less ulcerogenic than parent acids $^{21}$. It has also been found that copper complexes of some antiarthretic drugs are themselves more active as anti-inflammatory agents than their parent compounds $^{(22,23)}$.

Anti-inflammatory agents are classified as follows:

(A) Steroidal anti-inflammatory agents:

They exert their action by inhibiting the release of phospholipids in lipoxygenase pathway, which inhibits the release of arachidonic acid from membrane.

(B) Non-steroidal anti-inflammatory agents:

They are said to inhibit biosynthesis of prostaglandin endoperoxide synthase (PGHS) was isolated in 1976 $^{24}$ and cloned in 1988 $^{(25-27)}$. This membrane bound haemo- and glycoprotein has a molecular weight of 71 kd, and is found in the greatest amounts in the endoplasmic reticulum of prostonoid forming cell $^{28}$. It exhibits COX
activity, which both cyclizes arachidonic acid, and adds the 15-hydroperoxy group to form prostaglandin G2. The hydroperoxy group of prostaglandin G2 is reduced to the hydroxy group of prostaglandin H2 by a peroxidase that uses a wide variety of compounds to provide the requisite pairs of electrons. Both cyclooxgenase and hydperoxidase activities are contained in the same dimeric protein molecule.

The cyclooxgenase active site is a long, hydrophobic channel and Garvito and others 29 present arguments that some of the aspirin like drugs, such as flurbiprofen, inhibit COX-1 by excluding aracidonate from upper portion of the channel. Tyrosine 385 and serine 530 are at the apex of the long active site. Aspirin irreversibility inhibits COX-1 by acetylation of the serine 530, thereby excluding access for arachidonic acid 30. The S (-) stereoisomer of flurbiprofen interacts, via its carboxylate, with arginine 120, thereby placing the second phenyl ring within Vander Waals contact of tyrosine 385. There may be a number of other sub-sites for drug binding in the narrow channel.

The roetgenogram crystal structure of COX-2 closely resembles that of COX-1, and the binding sites for arachidonic acid on these enzymes are also very similar 31. The active site of COX-2 is slightly larger and can accommodate bigger structures than those, which are able to reach the active site of COX-1.

In a recent report, Chandrasekharan et al. 32 have described a third cyclooxygenase (COX-3) selectively inhibited not only by paracetamol but also by low concentration of some non- steroidal anti- inflammatory drug including aspirin. COX-3 is a variant of COX-1 which has retained
intron-1 dwing translation and which is found in human tissues in a polyadenylated form. Selective inhibition of COX-3 will discover potent and valuable new drugs for controlling pain and fever.

**Fig. 5.1** The “Inflammatory cascade”; Cyclooxygenase pathway of inflammation

There has been substantial progress in elucidation the mechanism of action of NSAIDs, although precise understanding of their therapeutic activities and side effects is still to be established. Inhibition of cyclooxygenase, the enzyme responsible for the biosynthesis of the prostaglandin and certain related autocoids is generally thought to be a major fact of the mechanism of non-steroidal anti-inflammatory drugs.
Some evidences show that prostaglandin participates in pathogenesis of the inflammation and fever and this reinforces the hypothesis that inhibition of the biosynthesis of these autocoids could explain a number of clinical actions. Numerous subsequent observations have substantiated this point of view including the discoveries that prostaglandin are released whenever cells are damaged. They appear in inflammatory exudates and NSAIDs inhibits the biosynthesis and release of prostaglandin in all cells tested.

There is a good deal of evidence that therapeutic dose of aspirin-like compounds reduce prostaglandin biosynthesis in man. Such doses inhibit the production of prostaglandin by human platelets and reduce the prostaglandin content of human serum, urine and synovial fluids of arthritic knee joints.

The theory of mode of action of NSAIDs is that the activation of phospholipase A2 induces release of arachidonic acid, which leads to the generation of some or all of the prostaglandin or thromboxanes. These compounds contribute in various ways to the genesis of inflammation, pain and fever. The NSAIDs inhibits cyclooxygenase step thereby preventing the formation of prostaglandin endoperoxidase (PGG₂ and PGH₂) and thromboxane A₂ and other prostaglandin and consequently reducing the signs and symptoms of inflammation 33.
5.3 SCREENING METHODS:

The screening method for anti-inflammatory activities have been classified as follows:

1. Non-immunological method
2. Immunological method
3. Miscellaneous method

1. Non-immunological method: This has been further divided into three types:

   (a) For evaluation of acute inflammation: It is of following types:

      i. Carrageenan hind paw edema method.
      ii. 5-hydroxy tryptamine induced hind paw edema method
      iii. Formalin induced hind paw edema method
      iv. Hyaluronidase induced hind paw edema method
      v. Histamin induced hind arthritis in knee joints method

   (b) For evaluation of subcutaneous inflammation: It is of following types:

      i. Carrageenan granuloma pouch technique
      ii. Cotton pellet granuloma technique

   (c) For evaluation of chronic inflammation: It is only one type:

      i. Formaldehyde induced arthritis method

2. Immunological Methods:

   This is of two types:

   (a) Adjuvent arthritis method and
   (b) Tubercullin sensitivity test method

3. Miscellaneous Method: It is of two types:
(a) UV erythema method\textsuperscript{42} and
(b) Urate crystal induced synovitia method\textsuperscript{43}.

The aim of the present investigation is to study the change in respective activities of the drugs due to the complex formation, hence to recommend the proposed complexes in the place of said drug for medicinal use in suitable cases.

5.4 EXPERIMENTAL

Anti-inflammatory activity of the complexes were performed using a plethysmometer to measure carrageenan induced rat paw volume following the method of Winter et.al.\textsuperscript{7}. Experimental methods are discussed in detailed in 2\textsuperscript{nd} section of chapter II.

5.5 ANTI-INFLAMMATORY ACTIVITY of MIXED LIGAND COMPLEXES

Piroxicam, Isoxicam, Aspirin and Diclofenac sodium are few of the most widely used NSAIDs. Their mode of action, based up on in vitro studies, is suggested to be inhibition of COX-2 which is the cytokine inflammatory inducible enzyme, while it’s action on physiologically responsive COX-1 is minimal\textsuperscript{44}. It is known that several NSAIDs act via chelation or by inhibiting the activity of metalloenzymes, but for most NSAIDs such as Piroxicam, Isoxicam, Aspirin and Diclofenac sodium little is known about how metalloelement bonding influence their activity. The anti-inflammatory activities of
PIROXICAM, ISOXICAM, ASPIRIN and DICLOFENAC and its metalloelement complexes \([\text{Fe(PIROXICAM)}_2(\text{H}_2\text{O})_2].2\text{H}_2\text{O}, \ \text{[Co(PIROXICAM)}_2(\text{H}_2\text{O})_2], \ \text{[Ni(PIROXICAM)}_2(\text{H}_2\text{O})_2], \ \text{[Cu(PIROXICAM)}_2(\text{H}_2\text{O})_2], \ \text{[Fe(ISOXICAM)}_2(\text{H}_2\text{O})_2], \ \text{[Co(ISOXICAM)}_2(\text{H}_2\text{O})_2], \ \text{[Ni(ISOXICAM)}_2(\text{H}_2\text{O})_2], \ \text{[Cu(ISOXICAM)}_2(\text{H}_2\text{O})_2], \ \text{[Fe(ASPIRIN)}_2(\text{H}_2\text{O})_2], \ \text{[Co(ASPIRIN)}_2(\text{H}_2\text{O})_2], \ \text{[Ni(ASPIRIN)}_2(\text{H}_2\text{O})_2], \ \text{[Cu(ASPIRIN)}_2(\text{H}_2\text{O})_2], \ \text{[Fe(DICLOFENAC)}_2(\text{H}_2\text{O})_2], \ \text{[Co(DICLOFENAC)}_2(\text{H}_2\text{O})_2]0.5\text{H}_2\text{O}, \ \text{[Ni(DICLOFENAC)}_2(\text{H}_2\text{O})_2].2\text{H}_2\text{O} \text{ and } \text{[Cu(DICLOFENAC)}_2(\text{H}_2\text{O})_2]_2.2\text{H}_2\text{O} \text{ were assayed by their ability to inhibit hind paw edema, the most frequently used test model for anti-inflammatory activity. Carrageenan-induced edema is an acute (non-specific) inflammation initiated and maintained by the release of histamine and serotonin and later by prostaglandins}^{45}. \text{The inhibitory effect of acid in NSAIDs such as PIROXICAM, ISOXICAM, ASPIRIN and DICLOFENAC is usually weak in the first phase of information, in contrast to their strong inhibition of the second phase. Almost all tested complexes exhibited a strong inhibitory effect on carrageenan-induced edema suggesting that they interfere with the release of histamine and serotonin and/or prostaglandin synthesis. Most NSAIDs inhibit the conversion of arachidonic acid to prostaglandin in vitro, but have little effect on the metabolism or arachidonic acid to leukotrienes(LTB) via the lipoxigenase pathway}^{44}.\)
5.5.1 Anti-inflammatory activity of PIROXICAM and its Fe(II), Co(II), Ni(II), and Cu(II) complexes:
PIROXICAM is a potent long acting NSAID with anti-inflammatory potency similar to indomethacin and analgesic potency greater than aspirin. It has useful antipyretic property. It is a reversible inhibitor of cyclooxygenase enzyme. It also decreases production of Ig rheumatoid factor and lowers it plasma level in patients of rheumatoid arthritis.

The results showing anti-inflammatory of PIROXICAM drug and its complexes with Fe(II), Co(II), Ni(II), and Cu(II) ions presented in Table 5.1. All the tested complexes except the complex of Fe(II) exhibited a strong inhibitory effect on carrageenan-induced edema than PIROXICAM suggesting that they interfere with the release of histamine and serotonin and/or prostaglandin synthesis.

Almost all the complexes of PIROXICAM tested showed high anti-inflammatory activity at molecular concentrations much lower than that of PIROXICAM. It is suggested that the anti-inflammatory activity of PIROXICAM is enhanced by coordination with metal.

5.5.2 Anti-inflammatory activity of ISOXICAM and its Fe(II), Co(II), Ni(II) and Cu(II) complexes:
ISOXICAM is one of the widely used NSAIDs therapeutically used in inflammatory and painful diseases of rheumatic and non-rheumatic origin. The anti-inflammatory activity of ISOXICAM and most of its other pharmacological effects are related to the inhibition of the
conversion of arachidonic acid to prostaglandins, which are mediator of various inflammatory processes.

The results presented in Table 5.2 shows the anti-inflammatory activity of ISOXICAM and its Fe(II), Co(II), Ni(II) and Cu(II) complexes. All most all the complex of ISOXICAM tested showed high anti-inflammatory activity at molecular concentrations much lower than that of ISOXICAM except complex of Fe(II), which is somewhat less potent than ISOXICAM.

The high anti-inflammatory activity at low molecular concentrations of Fe(II), Co(II), Ni(II) and Cu(II) complexes suggested that the anti-inflammatory activity of ISOXICAM is enhanced by coordination with metals

5.5.3 Anti-inflammatory activity of ASPIRIN and its Fe(II), Co(II), Ni(II) and Cu(II) complexes:

ASPIRIN possesses a number of properties that make it the most often recommended drug. It is an analgesic effective in pain relief. It is also an anti-inflammatory agent, providing some relief from the swelling associated with arthritis and minor injuries. ASPIRIN is also an antipyretic compound which means it reduces fever.

The anti-inflammatory activity of ASPIRIN and its Fe(II), Co(II), Ni(II) and Cu(II) complexes on carrageenan-induced edema revealed statistically significant anti-inflammatory activity close to ASPIRIN as shown in Table 5.3. All the tested complexes exhibit a strong inhibitory suggesting that they interfere with the release of histamine and serotonin
and/or prostaglandin syntheses. The anti-inflammatory activity of Co(II) and Cu(II) complexes were recorded very high at much lower molecular concentration than ASPIRIN. This suggested that the anti-inflammatory activity of ASPIRIN is enhanced by coordination with metal.

5.5.4 Anti-inflammatory activity of DICLOFENAC and its Fe(II), Co(II), Ni(II) and Cu(II) complexes:

DICLOFENAC is one of the widely used NSAIDs therapeutically used in inflammatory and painful diseases of rheumatic and non-rheumatic origin. The anti-inflammatory activity of DICLOFENAC and most of its other pharmacological effects are related to the inhibition of the conversion of arachidonic acid to prostaglandins which are mediators of the inflammatory process \(^{46,47}\). DICLOFENAC is a potent inhibitor of cyclooxygenase in vivo and in vitro; thereby decreasing the synthesis of prostaglandin, prostacyclin and thromboxane products.

The anti-inflammatory activity of DICLOFENAC and its 
\([\text{Fe(DICLOFENAC)}_2(\text{H}_2\text{O})_2]_2, \quad [\text{Co(DICLOFENAC)}_2(\text{H}_2\text{O})_2].0.5\text{H}_2\text{O},\]
\([\text{Ni(DICLOFENAC)}_2(\text{H}_2\text{O})_2].\text{H}_2\text{O}\) and \([\text{Cu(DICLOFENAC)}_2(\text{H}_2\text{O})_2]_2\cdot2\text{H}_2\text{O}\) complexes on carrageenan-induced edema revealed statistically significant anti-inflammatory activity close to DICLOFENAC (shown in Table 5.4). All the tested complexes except the complex of Fe(II) exhibited a strong inhibitory effect suggesting that they interfere with the release of histamine and serotonin and/or prostaglandin syntheses. All most all the complexes of DICLOFENAC tested showed high anti-inflammatory activity at much lower molecular concentrations than that
of DICLOFENAC. It is suggested that the anti-inflammatory activity of DICLOFENAC is enhanced by coordination with metal.

In conclusion, it is interesting to note that almost all Fe(II), Co(II), Ni(II) and Cu(II) complexes showed anti-inflammatory activity at much lower molecular concentrations than that of PIROXICAM, ISOXICAM, ASPIRIN and DICLOFENAC; in particular the complexes of Co(II), Ni(II) and Cu(II) were found to have a superior anti-inflammatory profile than PIROXICAM, ISOXICAM, ASPIRIN and DICLOFENAC; inhibiting inflammation mainly due to activation of lipoxygenase and/or complement systems. Fe(II) complex of PIROXICAM, ISOXICAM and DICLOFENAC possess some what less anti-inflammatory potency than their parent agent. It is suggested that the anti-inflammatory activity of PIROXICAM, ISOXICAM, ASPIRIN and DICLOFENAC are enhanced by the formation of coordination complex with transition metalloelement.
### Table 5.1: Anti-inflammatory Activity of PIROXICAM and it’s Complexes

<table>
<thead>
<tr>
<th>Compound</th>
<th>No. of animals used in each group</th>
<th>Dose (mg/Kg) body Wt.</th>
<th>Initial volume 0.0 h</th>
<th>Final volume after 3 h</th>
<th>Vol. of edema (final-initial)</th>
<th>% inhibition</th>
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<tbody>
<tr>
<td>Control</td>
<td>10</td>
<td>100</td>
<td>0.646</td>
<td>1.176</td>
<td>0.530</td>
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<td>0.749</td>
<td>0.950</td>
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<td>62.07</td>
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<td>[Fe (PIROXICAM)2(H2O)2].2H2O</td>
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<td>[Cu (PIROXICAM)2(H2O)2]</td>
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<td>0.615</td>
<td>0.783</td>
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### Table 5.2: Anti-inflammatory Activity of ISOXICAM and it’s Complexes

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<th>No. of animals used in each group</th>
<th>Dose (mg/Kg) body Wt.</th>
<th>Initial volume 0.0 h</th>
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<td>0.731</td>
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### Table 5.3: Anti-inflammatory Activity of ASPIRIN and its Complexes

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<th>No. of animals used in each group</th>
<th>Dose (mg/ Kg) body Wt</th>
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<th>Final volume after 3 h</th>
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<td>0.659</td>
<td>0.814</td>
<td>0.155</td>
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### Table 5.4: Anti-inflammatory Activity of DICLOFENAC and its Complexes

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<tr>
<th>Compound</th>
<th>No. of animals used in each group</th>
<th>Dose (mg/ Kg) body Wt</th>
<th>Initial volume 0.0 h</th>
<th>Final volume after 3 h</th>
<th>Vol. of edema (final-initial)</th>
<th>% inhibition</th>
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<td>0.530</td>
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<td>[Co(DICLOFENAC)$_2$ (H$_2$O)$_2$] 0.5 H$_2$O</td>
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<td>[Cu (DICLOFENAC)$_2$ (H$_2$O)$_2$] 2 H$_2$O</td>
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<td>0.694</td>
<td>0.811</td>
<td>0.117</td>
<td>77.92</td>
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5.6 References:


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SUMMARY